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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,081	11/09/2001	Didier Trono	CLFR:010US/TMB	2667

7590 12/01/2005

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,081	TRONO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,7-10,12,19,22,23,25,30-34 and 38-45* is/are pending in the application.

4a) Of the above claim(s) *11,13-18,20,21 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,7-10,12,19,22,23,25,30-34 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 08/26/05 has been acknowledged.

Claims 1-3, 6, 26-29 and 35-37 are canceled.
Claims 11, 13-18, 20-21 and 24 are withdrawn.
Claims 4-5, 7-10, 12, 19, 22, 23, 25, 30-34 and 38-45 are examined.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Election/Restrictions

This application contains claims 11, 13-18, 20-21 and 24 drawn to an invention nonelected with traverse in Paper No. 03/31/04. *A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action* (37 CFR 1.144) See MPEP § 821.01.

Double Patenting

Claims 4-5, 7-10, 12, 19, 22-23, 25, 30-34 and 38-45 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-123 of copending Application No. 10/261,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of transduced host cells and the method of transducing human hematopoietic

stem cells as claimed in the 10/261,078 encompasses the host cells and method of transducing human hematopoietic stem cells as claimed in instant application (10/010,081), for the same reasons of record as set forth in the office action mailed on 03/24/05

Specifically the scope of host cell of claims 113-115 of '078 is identical to the host cells (hematopoietic progenitor cells) of claims 4-10, 12, 19, 22-23, 25, 30-34 and 38-45 of instant application. In addition the scope of method of transducing human hematopoietic stem cells with a lentiviral vector of claims 116-123 of '078 is identical to claims 32-34 and 38-45 of instant application. Thus the invention as claimed in the '078 and the instant application are obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to argument

The applicant argues that the instant application is in condition of an allowance while '078 is still pending. The double patenting rejection is maintained, since the instant application is not in condition of an allowance.

Claim Rejections - 35 USC § 103

Claims 4-5, 7-8, 12, 25, 30-34 and 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998 in view of Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999), for the same reasons of record as set forth in the office action mailed on 03/24/05.

Zufferey teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes (page 9873, abstract, col.2 para.1; page 9874, col.1 paras 3-7). The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR (page 9874, col.2 para.5, page 9875, table-1, page 9876, table-2, page 9877 table-3). The cited art

further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable transcription of a transgene in human hematopoietic progenitor cells upon transduction with a lentiviral vector (*see Case et al PNAS 96:2988-2993, 1999, ref. of record on PTO-1449*). In addition the cited art teaches transduction of human PBLs and human lymphocytic SupT1 cells using the SIN expression vector (page 9875, table-1; page 9878 fig-4). The cited art further teaches that inactivation of LTR provides higher signal to noise ratio which falls in the range of about 10 to about 200 (see page 9876 table 2).

Even though Zufferey teaches transduction of human PBLs the cited art does not teach the transduction of hematopoietic stem cell comprising a self-inactivating SIN-lentiviral vector wherein the transgene is a multidrug resistance gene (MDR).

Deisseroth teaches clinical trails involving multidrug resistance transcription units encoded in retroviral vectors. The cited art teaches the use of retroviral vectors to transfer human MDR-1 into human hematopoietic stem cells in-vitro (page 1607, col. 1 para 4; col. 2 para.2). The cited art further teaches clinical trials, which show engraftment of vector modified clonogenic hematopoietic progenitor cells into human patients (page 1608, col.1). The cited art further teaches the use of lentiviral vectors to transduce early hematopoietic stem cells, which resulted in the transduction of at least 80% of CD34+/CD38- hematopoietic stem cells (page 1608, col.2 para.d). In addition the cited art teaches o of clonal analysis (differentiation) of CD34+ CD38- transduced cells cultured in LTBMC culture media for long-term cultures (page 2889, col.2 para.5-6, page 2991, fig-3, page 2992 col.1).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zufferey by substituting the GFP reporter gene with a MDR gene and hematopoietic cells with hematopoietic stem cells in view of Deisseroth. It would have been further obvious to differentiate the transduced stem cell into different lineages, since hematopoietic stem cells have clonogenic

potential. One would have been motivated to do so, since the transduction of human hematopoietic progenitor cells with the MDR-gene decrease the toxicity of chemotherapeutic agents in hematopoietic cells and differentiated cells. One would have a reasonable expectation of success in doing so, since retrovirus induced transduction of human progenitor cells (to express a gene of interest) has been routine in the art at the time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

In response filed on 08/26/05 the applicant argues that claim 30 has been amended to the use of a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in both a human hematopoietic progenitor cell and a differentiated hematopoietic cell. The applicant furhter argues that Zufferey does not appear to include any data showing the backgound present in a control cell, so it could not reasonably be expected to teach or suggest a signal-to- noise parameter. The applicant furhter argues that Zufferey teaches transduction of HeLa, HeLa-tat, and 293T cells lines which are not human hematopoietic progenitor or differentiated hematopoietic cells. Regarding cliam 32 the applicant argues that claim 32 has been amended to the use of a promoter that is capable of promoting expression of the transgene at a siral-to-noise ratio of between about 10 and about 200 in both a human hematopoietic progenitor cell and a differentiated hematopoietic cell. The applicant argues that claim 32 as amended now includes furhter step of differentiating the transduced stem cells into a differentiated hematopoietic cells.

However, regardig signal to noise ratio the applicants arguments are found not persuasive because Zufferey teaches the use of a self-inactivating recombinant lentiviral vector containing an inactivated LTR and CMV promoter, which is all that is required to make a transduced human hematopoietic progenitor cell of instant claims to elicits the transgene expression with low background. A recitation directed to the manner in which a claimed apparatus is intended to be used does not distinguish the claimed apparatus from the prior art if the prior art has the capability to so perform see

MPEP 2114 and *Ex parte Masham* 2 USPQ2d 1647 (1987). In instant case the cited art clearly teaches use of SIN-vector as required by instant claims because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02. In instant case the self-inactivating recombinant lentiviral vector containing an inactivated LTR and CMV promoter is inherently capable of providing a signal to noise ratio between about 10 to about 200 in transduced host cell. Zufferey clealry teaches that inactivation of LTR decrease the endogenous transgene experession in host cells see page 9877 co.2 para.3). The applicant fails to consider figure-4 page 9878, which clealry teacehs that inactivation of LTR promoter in a SIN-vector redduces the endogenous LTR activity which is capable of providing higher signal to noise ratio. In addition the signal to noise ratio is an arbitrary value that not only depends upon the strength of transgene signal by is also a function of instrument sensitivity and settings. Furthermore, preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).*

Regarding transduction of hematopoietic stem cells and their differentiation the combined teaching of Zufferey and Deisseroth clearly teaches transduction of hematopoietic stem cells using a SIN-retroviral vector and differentiation thereof in-vivo after transplantation or in-vitro using clonogenic assays (see Deisseroth). Furthermore there is a reasonable expectation of success to use SIN-lentiviral vector to transduce hematopoietic stem cell, since retroviral mediated transduction of human progenitor cells (to express a gene of interest) has been routine in the art at the time of instant

invention because it has been well established in the art at the time the instant invention was filed, that the lentiviral vectors are capable of transducing non-dividing hematopoietic stem cells. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Chang et al (Gene Therapy 6;715-728, 1999), for the same reasons of record as set forth in the office action mailed on 03/24/05.

As stated above the combined teaching of Zufferey and Deisseroth teaches transduciton of a human hematopoietic stem cell using self-inactivating HIV-1 based lentivirus vector (SIN). Even though Zufferey and Deisseroth teaches a hematopoietic stem cell transduced with self-inactivating HIV-1 based lentivirus vector, the cited art dose not teach a lentiviral vector, wherein the EF-1α promoter directs the expression of a transgene.

Regarding claims 9-10 specifically, Chang teaches a HIV-1 derived vector system comprising pTVΔEFGPF genetic construct, which comprises human eleongation factor 1α promoter (page 126, col.1 para.1, line 21-26). The cited art further teaches the transduction of human CD34+ hematopoietic stem cells using pTVΔEFGPF lentiviral vector, wherein the transduced progenitor cells express the GFP transgene under the control of the human eleongation factor 1α promoter (page 718. col.2 para. 2; pager 723, fig-5). Regarding claims 6-8 the cited art teaches that human hematopoietic progenitor cells express the the GFP transgene expression under the control of an EF-1α promoter, wherein the signal to noise ratio of the expressed GFP falls with the range of about 10 and about 200 (page 723, fig-5 see inset a-d). The cited art disclose that the phase contrast microscopy reveled that the strength of GFP signal is significantly higher

than the untransduced colony (inset-a, lower colony). Such a contrast certainly fall in the range of signal to noise ratio as claimed (between about 10 and about 200). The signal to noise ratio is an arbitrary value that not only depends upon the strength of transgene signal by is also a function of instrument sensitivity and settings. Therefore the cited art clearly teaches that the EF-1α promoter provides transgene expression with higher signal to noise ratio in human hematopoietic progenitor cells. In addition, the cited art clearly anticipate the invention as claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the self-inactivating HIV-1 based lentivirus vector of Zufferey by substituting the CMV promoter with human elongation factor 1α promoter for the transduction of human hematopoietic stem cells. One would have been motivated to do so because the EF-1α promoter is strong promoter to regulate the expression of a transgene in primary CD34+ hematopoietic stem cells. One would have a reasonable expectation of success of success in doing so, since substituting a promoter sequence with another and transduction of hematopoietic stem cells using a lentiviral vector has been routine in art at time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

The applicant arguments regarding prior issue on pages 3-4 of response filed on 0/26/05 has been fully considered. The applicant argues that there is no motivation to combine the teachings of Chang with Zufferey, in that there was no reasonable

expectation that the SIN-design would work in hematopoietic cells. The applicant argues that SIN design incorporate modification in LTR and there was simply no way of knowing in advance what effect this would have on its ability to express in hematopoietic stem cells. The applicant argues that even though Chang demonstrate use of EF-1α promoter in a lentiviral vector in context of CD34+ cells the vector as taught by Chang is not SIN vector. The applicant furher argues that Chang fails to demonstrate whetehr EF-1α promoter would remain active in differentiated hematopoietic cell.

However, applicant's arguments are found not persuasive because as stated in the earlier office action the composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02. In instant case Chang clearly teaches the transduction of human CD34+ hematopoietic stem cells using pTVΔEFGPF lentiviral vector, wherein the transduced progenitor cells express the GFP transgene under the control of the human eleongation factor 1α promoter (page 718. col.2 para. 2; pager 723, fig-5). The applicant fails to consider that the clonogenic assay presented in figure-5, page 723 represent differentiated CD34+ cells after lentiviral transduction. Therefore Chang clealry demonstrates that EF-1α promoter remains active in differentiated hematopoietic cell. In addition one would have a reasonable expectation of success in making a SIN-designed vector containing the EF-1α promoter, since substituting a promoter sequence with another and transduction of hematopoietic stem cells using a lentiviral vector has been routine in art at time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Zufferey et al (J. Virol. 73(4):2886-2892, 1999, ref. of record on PTO-1449).

As stated above the combined teaching of Zufferey and Deisseroth teaches transduciton of a human hematopoietic stem cell using self-inactivating HIV-1 based lentivirus vector (SIN). However Zufferey-1998 does not teach a SIN vector comprising the virus posttranscriptional regulatory element that promotes the expression of a transgene, wherein the posttranscriptional regulatory element is woodchuck hepatitis virus posttranscriptional regulatory element (WPRE).

Zufferey-1999 teaches a HIV-1 based retroviral vector (pHR' CMV-GFP) that contains woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). see page 2887 fig-1A, col.2 para. 2). The cited art further teaches that WPRE enhances the expression of a transgene in host cells transduced by the HIV-based vectors (page 2888, fig-2, col.2 results).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zefferey-1998 by incorporating posttranscriptional regulatory element obtained from woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) in view of Zufferey-1999. One would have been motivated to do so to increase the levels of expression of a transgene in host cells. One would have a reasonable expectation of success in doing so, since genetic modification of lentiviral vectors has been routine in the art at time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

The applicant arguments regarding prior issue on page 5, lines 1-5 of response filed on 08/26/05 has been fully considered but has been found not persuasive for the

reasons of record and as set forth above in arguments regarding claims 4-5, 7, 8, 12, 25, 30-34 and 38-45 above.

Claim Rejections - 35 USC § 112

The rejection of claims 6-8 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicants arguments filed on pages 5-6 in response filed on 08/26/05.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633